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Eosinophilic fasciitis associated with hypereosinophilia, abnormal bone-marrow karyotype and inversion of chromosome 5

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Summary

We report the case of a male patient presenting with eosinophilia, pulmonary oedema and eosinophilic fasciitis (EF). He had the classic clinical appearance and magnetic resonance imaging of EF. Cytogenetic analysis of the bone marrow revealed a previously undescribed pericentric inversion of chromosome 5. Overall, the presentation was consistent with a diagnosis of chronic eosinophilic leukaemia, not otherwise specified (CEL-NOS). Dermatologists should consult a haematologist in cases of EF, in order to rule out possible haematological malignancies.

Eosinophilic fasciitis (EF) is characterised by erythematous, indurated plaques of the skin and subcutaneous tissue, often on the legs. Classic histological findings are described on deep fascial biopsy and also on magnetic resonance imaging (MRI) scanning. The disease has been found in association with strenuous exercise, insect bites, drug reactions and various haematological malignancies including, as in this case, chronic eosinophilic leukaemia, not otherwise specified (CEL-NOS). Analysis of our patient's bone marrow revealed a previously undescribed pericentric inversion of chromosome 5. Loci involving genes coding for interleukin (IL)-3 and IL-5 are likely to be involved in the breakpoint. This case affirms the role of the haematologist in cases of EF.

Report

A 69-year-old man presented with a 4-month history of skin erythema, swelling of his legs and torso, and weight gain. Over the preceding month, he had grown breathless and increasingly tired, and chest radiography suggested pulmonary oedema. The patient was admitted to hospital and underwent diuresis with furosemide, resulting in his weight dropping from 108 to 89 kg. Initial investigations included aechocardiography, abdominal ultrasonography, and computed tomography of the chest, abdomen and pelvis, all of which gave normal results. Full blood count showed raised levels of eosinophils (2.3×10^9/L; normal range 0.1–0.8 $\times 10^9$/L) white blood cells (9.5×10^9/L; 4.0–11.0 $\times 10^9$/L) and platelets (493×10^9/L; 150–450 $\times 10^9$/L). Haemoglobin was within the normal range (125 g/L; 120–160 g/L). Levels of autoantibodies including antinuclear antibody, double-stranded DNA, rheumatoid factor and immunoglobulins were normal. There was no sign of allergy, parasitic infection or a drug reaction. The patient was referred to the haematology and dermatology physicians for opinions.

On physical examination, the patient was found to have widespread erythema and marked pitting oedema over his limbs and torso, and he reported feeling stiff and itchy. There was no history of weight-lifting, dysphagia or insect bites, nor were there signs of sclerodactyly, Reynaud phenomenon or calcinosis.[1] A skin biopsy was taken to exclude the possibility of Wells syndrome, or an infiltrative process secondary to malignancy. However, the results were inconclusive, demonstrating only scant dermal eosinophils. The sample did not include the deep fascia.

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Over the following weeks, the patient's skin took on the classic appearance of EF, with hair loss extending over the limbs and symmetrical thickening of the deep tissues of both legs, limiting his ankle movement (Fig. 1). The patient also had marked guttering over the superficial veins of both arms when these were raised (described as the 'groove sign' of EF).[2] The patient was reluctant to undergo fascial biopsy. However, an MRI scan of his lower legs demonstrated classic findings of EF, with high signal from the fascia surrounding normal soleus and gastrocnemius muscles (Fig. 2).[3]

Peripheral blood examination showed eosinophilia but no evidence of T-cell clonality.

A bone-marrow biopsy was normocellular, with trilineage haemopoiesis and no dysplastic features. Eosinophils and their precursors accounted for 20–25% of total myeloid activity (normal range 0.0–7.0%) (12–16% of total nucleated cells). Myeloblasts were not increased (< 1%). Cytogenetic bone-marrow analysis demonstrated the presence of an abnormal clone with a pericentric inversion of chromosome 5 (inv(5)(p1?3q3?5)) (Fig. 3), which was found in 9 of 25 examined cells. This particular chromosomal abnormality has not been previously reported.

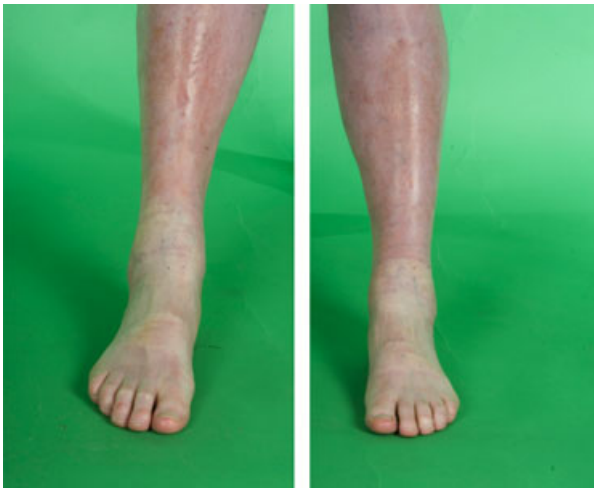

Figure 1 Taut, shiny appearance of both lower legs shortly after presentation.

These findings were consistent with a diagnosis of CEL-NOS. The patient was started on prednisolone (initially 60 mg daily, which resulted in improvement of the systemic symptoms, fluid overload, dermatological changes and eosinophilia.

EF was first described by Schulman in 1975.[1] It is characterized by deeply indurated, bound-down plaques of skin and subcutaneous tissue, often on the limbs. EF has been described in association with oedema and erythema at initial presentation. The absence of Reynaud phenomenon and sclerodactyly distinguishes EF from scleroderma. EF is associated with peripheral eosinophilia, hypergammaglobulinaemia and increased erythrocyte sedimentation rate. Characteristic changes are observed on deep fascial biopsy.[4] Classic MRI scan findings are well described, and correlate with disease activity.[3]

The aetiology of EF is poorly understood, but it has been reported following strenuous exercise, insect bites, various drugs, bone-marrow transplantation and trauma.[5] EF is also associated with a wide variety of haematological disorders, including CEL, idiopathic hypereosinophilia, multiple myeloma, Hodgkin lymphoma, immune thrombocytopenia and aplastic anaemia.

Possible treatment of EF with the IL-5 inhibitor interferon-alfa has been suggested.[6] Although the cytogenetic abnormality observed in our patient has not been described previously, the breakpoint on 5q is close to the location of the platelet-derived growth factor receptor-β (*PDGFRB*) gene, which is associated with

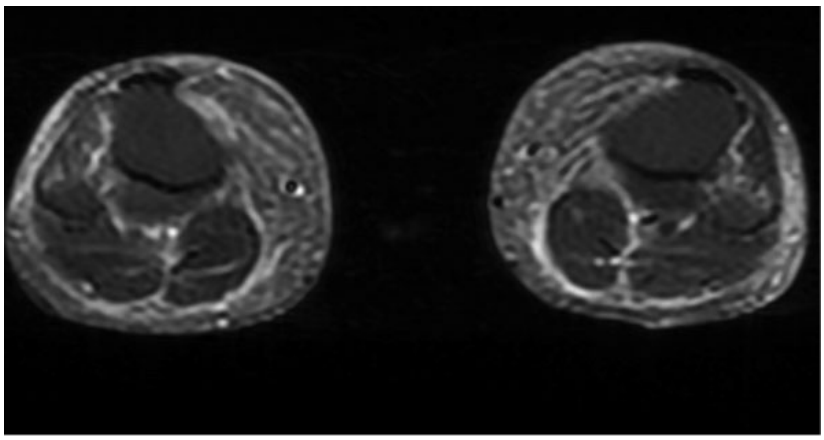

Figure 2 Axial plane magnetic resonance images of the lower legs showing high signal in the superficial fascia. Bone and muscle appearances are normal.

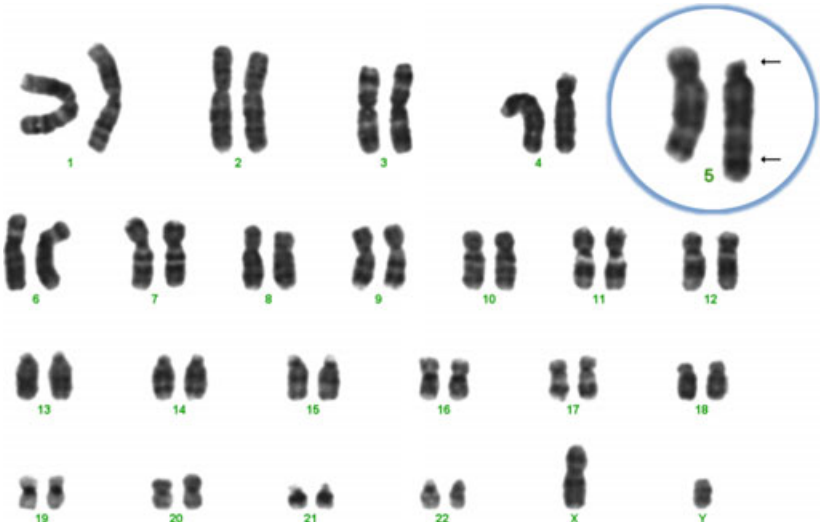

Figure 3 Chromosome 5 showing abnormal pericentric inversions (this is a rearrangement that includes the centromere and has a breakpoint in each arm, as indicated by arrows).

eosinophilia. Fluorescence *in situ* hybridization showed this gene was not involved in our case; however, the loci for the interleukin genes IL-3 and IL-5 are also close to this location on 5q. These cytokines influence eosinophil differentiation, and levels of both IL-3 and IL-5 have been found to be raised in cases of eosinophilia.[5,7]

CEL is a myeloproliferative neoplasm characterized by clonal proliferation of eosinophil precursors. Cases resulting from rearrangement of the *PDGFRA*, *PDGFRB* or *FGFR1* genes (encoding for PDGFR-α, PDGF-β and fibroblast growth factor receptor, respectively) are separately identified in the most recent World Health Organization classification of CEL. Cases without these gene rearrangements are classified as CEL-NOS. In CEL-NOS, there is a peripheral blood eosinophil count of $> 1.5 \times 10^9$/L, with evidence of eosinophil clonality, abnormal cytogenetics or an increase in peripheral blood or bone-marrow myeloblasts,[8,9] as found in our case. Although CEL may be asymptomatic, patients can experience fever, fatigue and myalgia, as well as cardiac, dermatological, pulmonary, neurological or gastrointestinal symptoms. Dermatological symptoms include angio-oedema, urticaria, Wells syndrome, vasculitis, erythroderma, blisters and EF. Tissue damage follows tissue infiltration by eosinophils with subsequent degranulation, releasing cytotoxic proteins.[9]

In our patient, EF appears to have been part of a broader syndrome of CEL-NOS occurring as a result of an abnormal bone-marrow clone. The chromosome inversion described is close to the IL genes involved in eosinophil recruitment and activation. This discovery gives us a new insight into EF and hypereosinophilia, and also lends weight to the notion of treating EF with IL-5 inhibitors such as interferon-alfa and the anti-IL5 monoclonal antibody mepolizumab.

In general, EF has been described as occurring in isolation, and although most cases do have systemic peripheral blood eosinophilia, it is rarely investigated with a bone-marrow biopsy. In 2003, Fujii *et al.* published a report on eosinophilic cellulitis and its relationship to the hypereosinophilic syndrome.[10] These authors suggested that it might be incorrect to consider eosinophilic cellulitis a separate entity, and that investigations for underlying haematological disease should be performed. Similarly, we propose that EF may also be part of a broader spectrum of hypereosinophilic disease. We further suggest that more thorough investigation of EF, including referral to a haematologist, may reveal an underlying haematological disease, with consequent implications for management.

Learning points

- EF may be associated with haematological malignancies.
- EF may also be associated with bone-marrow karyotype abnormalities, including this previously undescribed inversion of chromosome 5.
- In our case, the chromosome 5 gene may be involved with IL-5, which is known to be associated with eosinophilic disorders.
- Interferon-alfa, an IL-5 antagonist, and mepolizumab, an anti-IL5 monoclonal antibody, have been suggested as therapy for EF.

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